PATENTS
Attorney Docket No. 08446-0002

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Derek P. Freyberg 12/27/04
Derek P. Freyberg Date

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re Application of:

Robert C. Corcoran

App. No.: 09/975,~~528~~ 258

Filed: 12 October 2001

Confirmation No.: 8853

Art Unit: 1723

Examiner: Ernest G. Therkorn

For: Purification of substances by reaction affinity chromatography

Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

Sir:

TRANSMITTAL

Transmitted herewith for filing in the above-identified application are:
Credit card payment form (PTO-2038), 1 page
Appeal Brief, 26 pages
Total, with this Transmittal, 28 pages.

The fee for the filing of the Appeal Brief and for a five-month extension of time for its filing, and any other necessary fees, are authorized to be charged to a credit card (form PTO-2038 attached).

Respectfully submitted,

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27 December 2004

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APPEAL BRIEF

On 24 May 2004, Appellant filed a Notice of Appeal from the Final Rejection mailed 25 November 2003 in this application. A five-month extension of the period for filing the Appeal Brief is requested in the accompanying Transmittal and the fee is authorized to be paid by credit card in the accompanying PTO-2038, so that the period for filing expires on 27 December 2004 (24 December being a Federal holiday, and 25 and 26 December being a Saturday and Sunday respectively).

The following constitutes Appellant's Brief on Appeal under 37 CFR 41.37.

(i) Real party in interest

The real party in interest is the inventor, Dr. Robert C. Corcoran; the application is unassigned.

(ii) Related appeals and interferences

There are no related appeals or interferences.

(iii) Status of claims

Claims 79-140 are in this application, claims 1-78 having been cancelled.

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The claims were subject to a restriction requirement, and claims 82-86, 92, 95-98, 100, 102, 110-113, 117-120, 124-127, and 129-140 were withdrawn from examination. The restriction requirement was traversed in the response of 14 May 2003, but was made final.

Claims 79-81, 87-91, 93, 94, 99, 101, 103-109, 114-116, 121-123, and 128 are under examination and were finally rejected. The rejection of these claims is appealed.

(iv) Status of amendments

No amendment was filed subsequent to the final rejection.

(v) Summary of claimed subject matter

The two independent claims involved in this appeal are claims 79 (generic) and 128 (specific to the isolation of thebaine).

The invention of the present application, as claimed in claims 79-140, and in particular as claimed in claims 79-81, 87-91, 93, 94, 99, 101, 103-109, 114-116, and 121-123, claims that are the subject of this appeal, is a method of separating a target from a sample composition containing the target, by:

(a) contacting the sample composition with a reactive affinity molecule attached to a phase separating group, the reactive affinity molecule comprising a reactive functional group, and the reactive affinity molecule reacting with the target to form an adduct by forming a covalent bond between the target and the reactive functional group, where the reaction forming the adduct is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond;

(b) separating the adduct from the sample composition;

(c) contacting the adduct with an eluent to regenerate the target and the reactive affinity molecule; and

(d) separating the target from the reactive affinity molecule.

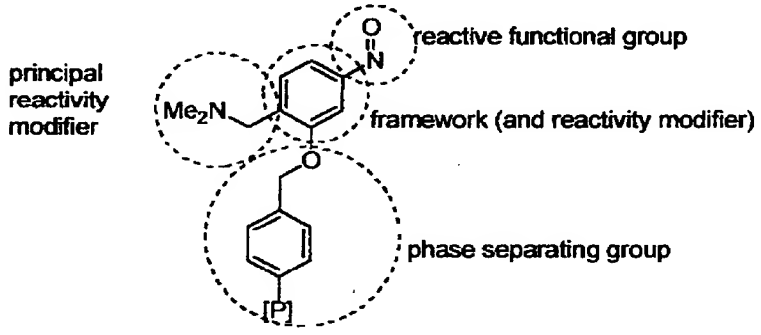
The invention as claimed in claim 128 is a method for isolating thebaine from a sample composition comprising contacting the composition with a reactive affinity molecule that is a substituted nitrosobenzene. It is an example of step (a) of claim 79; but claim 128 does not require steps (b) to (d) of claim 79.

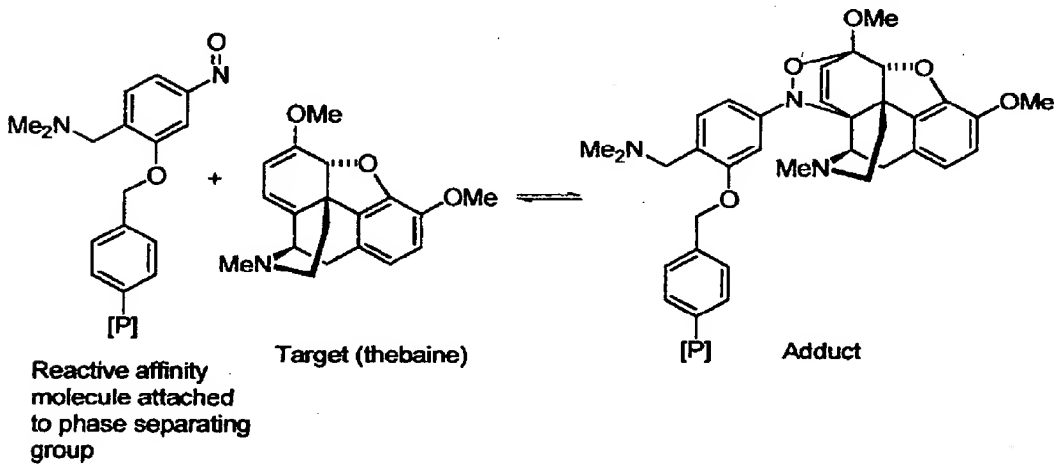
The method described in the application and claimed broadly in claim 79, referred to by Appellant as reaction (or reactive) affinity chromatography, relies on the reversible formation of a covalent bond between the target and the reactive functional group of a reactive affinity molecule attached to a phase separating group (e.g. the reversible formation of a covalent bond between the target and a "stationary phase" – to use the language of column chromatography), separation of the adduct from the sample composition (because the adduct is bound to the stationary phase and the remainder of the sample composition is not), the subsequent spontaneous reversal of the covalent bond formation to regenerate the target *and the reactive affinity molecule* from the adduct (since the reaction is reversible), and the separation of the target from the reactive affinity molecule.

The technique is summarized at paragraph **[002]** of the application, and further at paragraphs **[0018]** to **[0020]** and **[0024]**, and illustrated conceptually in Figure 1. The term "reaction affinity

chromatography" appears in the title of the application, and the term "reactive affinity chromatography" and abbreviation "RAC" appear in paragraph **[0035]**, with a more detailed discussion of its operation in paragraphs **[0036]** to **[0039]**, where paragraph **[0038]** (and also paragraph **[0071]** disclose recovery of a target by elution, including the use of an eluent to change the equilibrium constant of the reaction forming the covalent adduct, such as by interaction of the eluent with the reactivity modifier. The term "naturally reversible reaction" is defined in paragraph **[0048]**.

With respect to claim 128, this isolation is described at paragraph **[0070]** and illustrated at Figure 3 (showing the reversible formation of the adduct). The formation of the elected reactivity affinity molecule (containing a polystyrene-based ion exchange resin-immobilized nitroso group, where the substituents Y and Z of paragraph **[0070]** and Figure 3 are H and dimethylaminomethyl respectively) is described at paragraphs **[0112]** to **[0115]** and illustrated at Figure 6, while the use of a pH change to decrease affinity is described at paragraphs **[0118]** to **[0120]** and substantially illustrated at Figure 5 (affinity decrease by positive to neutral Rmod conversion), replacing the cyclohexadiene of that Figure with thebaine as discussed in paragraph **[00116]**.





It should be noted that all of the reactions involved in the formation of the covalent bond are reversible in the classic sense (they regenerate the original reactants), as illustrated above for the

formation of the Diels-Alder adduct with thebaine. This should be distinguished from covalent chromatography and like techniques in which, although one of the reactants is regenerated, the other is not, but is converted by the regeneration process into some new molecule.

(vi) Grounds of rejection to be reviewed on appeal

A. Claims 79, 80, 87-91, 93, 94, 99, 101, 103-109, 114-116, and 121-123 were rejected under 35 USC 112, ¶1 as containing new matter.

There are 11 art rejections in the final rejection. These have been regrouped so that rejections of the same claims are discussed together, and are numbered in bold within each subsection here in the order in which they appear in the final rejection.

B. **(1)** Claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 were rejected under 35 USC 102(b) as anticipated by, or under 35 USC 103(a) as obvious over, Hylarides et al., US Patent No. 5,141,646 ("Hylarides").

C. **(6, 7)** Claims 79, 80, 87-91, 93, 94, 106, 107, 114-116, 121, and 122 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn et al., US Patent No. 6,362,008 ("Kohn"). [Two separate rejections were made on page 6 of the Final Rejection - the first **(6)** being of claims 115, 116, and 122, and the second **(7)** of claims 79, 80, 87-91, 93, 94, 106, 107, 114-116, 121, and 122; but the reasons given were identical and the second encompasses the first, so the two are discussed together.]

D. **(2)** Claims 81, 123, and 128 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of either Schössler et al., US Patent No. 4,822,681 ("Schössler") or Carron et al., PCT Publication No. WO 98/59234 ("Carron") and Sohar et al., US Patent No. 3,894,026 ("Sohar"). **(8)** Claims 81, 123, and 128 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of either Schössler or Carron and Sohar.

E. **(3)** Claim 91 was rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Stevens et al, US Patent No. 4,927,539 ("Stevens") and Schössler. **(9)** Claim 91 was rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of Stevens and Schössler.

F. **(4)** Claims 99, 101, and 103-105 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Carron or Duran et al., PCT International Publication No. WO 99/16907 ("Duran"). **(10)** Claims 99, 101, and 103-105 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of Carron or Duran.

G. **(5)** Claims 108 and 109 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of either Schössler or Carron. **(11)** Claims 108 and 109 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of either Schössler or Carron.

For each ground of rejection, all claims subject to that rejection stand or fall together; except that in section D., the rejection of claims 81, 123, and 128, claim 128 is treated separately because unlike the other claims it claims only the contacting of a target (thebaine) and a reactive affinity

molecule (a modified nitrosobenzene) and not the subsequent regeneration of the target and reactive affinity molecule.

(vii) Argument

A. Claims 79, 80, 87-91, 93, 94, 99, 101, 103-109, 114-116, and 121-123 do not contain new matter

Claims 79, 80, 87-91, 93, 94, 99, 101, 103-109, 114-116, and 121-123 were rejected under 35 USC 112, ¶1 as containing new matter, with the final rejection stating that support could not be found in the application as filed for the claim language "without the addition of a reagent acting at the covalent bond." Reversal of this rejection is requested.

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. Amendments to an application which are supported in the original description are not new matter. Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Appellant agrees that the application as filed does not provide *in haec verba* support for the objected-to language; however: (a) the application as filed is not required to provide *in haec verba* support as long as the language finds clear support in the application as filed (*see* the discussion above), and (b) the application as filed does provide such clear support.

First, the reactive affinity chromatography (RAC) method of the invention is always discussed in the application as filed as involving a "naturally reversible reaction" (see for example

claim 1 as filed) forming the adduct. Such a reaction is defined in paragraph **[0048]** as follows: "Naturally reversible reaction, as used herein, is a reaction that can reverse itself without the addition of any additional chemical reagents," i.e. it is a reaction that is reversible under the conditions of the contacting, and is also defined in paragraph **[0048]** as being a reaction forming a covalent bond between the reactive functional group (RFG) of the reactive affinity molecule (RAM) and the target to form an adduct. Thus the application provides clear support for the concept that a naturally reversible reaction is one that can reverse itself under the conditions of the contacting without the addition of any additional chemical reagents, and therefore without a reagent acting at the covalent bond, as now expressed in claim 79.

Beyond this, there are two broad cases that can be addressed: those in which the eluent remains constant, and those in which the eluent is changed to modify the affinity of the RAM for the target.

Where the eluent is constant, since the reaction is naturally reversible, it is reversible without the addition of any reagent, and therefore without the addition of a reagent acting at the covalent bond. A more phenomenological justification may be seen at paragraphs **[0038]** and **[0071]**, where a simple version of the RAC method involves recovering the target by simple elution. Since the RAC method inherently involves formation of a covalent bond, and simple elution does not involve the addition of any reagents, "the reaction forming the adduct is reversible under the conditions of the contacting without addition of a reagent acting at the covalent bond," as required by claim 79, and such a reaction is clearly disclosed in the application as filed.

Where the eluent is changed in some fashion to effect a change in the affinity of the reactive functional group for the target, it is clear from the application at paragraphs **[0084]** to **[0090]** that change in properties of the eluent effects a change on the reactivity modifying group, the RMod, rather on the naturally reversible reaction that forms the basis of the RAC process (i.e. the eluent does not act on the covalent bond forming the adduct itself, but on the RMod). Since the RMod is not the same as the RFG or target, nor the adduct resulting from their reaction, the process of bond-forming/bond-breaking occurs without addition of a reagent acting at the covalent bond, and thus also, in the words of claim 79, "the reaction forming the adduct is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond." Since the RAC method also contemplates the change of an eluent, which is the addition of a reagent that modifies the RMod, it is clear that the "naturally reversible reaction" of claim 1 as filed is a reaction "reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond."

Thus the application as filed, by defining the RAC reaction as naturally reversible and by also permitting the change of an eluent so that such a reaction may also be influenced by a reagent acting on the RMod, provides clear support for the use in claim 79 of the language "reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond."

The final rejection responds to Appellant's arguments but fails to address them. First, it states that Appellant's arguments "urge that support can be found for 'without the addition of a reagent acting at the covalent bond'" in paragraph **[0048]** but that that paragraph does not provide support for the phrase. This conclusory statement simply ignores Appellant's arguments made above, as no contradictory reasoning is given. Second, the final rejection states that Appellant's arguments "urge that support can be found for 'without the addition of a reagent acting at the covalent bond" in paragraphs **[0038]**, **[0071]**, and **[0084]** to **[0090]** directed to the use of an eluent, but that "an eluent

would appear by definition to be a reagent that removes the target molecule from the affinity molecule. This is particularly apparent in applicant's example of using a pH modifying agent as an eluent. As such, no support can be found for 'without the addition of a reagent acting at the covalent bond'." This misses the point. An eluent is indeed a reagent that removes the target molecule from the affinity molecule by providing at least a solvent to physically separate the target molecule from the reaction affinity molecule when the reaction forming the adduct is reversed, but this is the property of all eluents (*see* the discussion of "eluant" at paragraph **[0050]**, and note that the eluents described there are all of the kind that would conventionally be considered non-reactive). The eluent may also change the equilibrium constant of the reaction between the target molecule from the affinity molecule (*see* paragraph **[0053]**, and the discussion of affinity modification at paragraphs **[0084]** to **[0090]**). But it is always true that the reaction between the target molecule and the affinity molecule should be naturally reversible (i.e. reversible without the addition of an external reagent), and so this eluent must not act at the covalent bond, and indeed it is suggested that it may act at the Rmod to thereby influence the adduct-forming reaction. Thus the application as filed, by defining the RAC reaction as naturally reversible and by also permitting the change of an eluent so that such a reaction may also be influenced by a reagent acting on the RMod, provides clear support for the use in claim 79 of the language "reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond."

Thus claims 79, 80, 87-91, 93, 94, 99, 101, 103-109, 114-116, and 121-123 do not contain new matter.

B. Claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 are neither anticipated by nor obvious over Hylarides

Claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 were rejected under 35 USC 102(b) as anticipated by, or under 35 USC 103(a) as obvious over, Hylarides et al., US Patent No. 5,141,646 ("Hylarides"). Reversal of this rejection is requested.

The claimed invention

The invention of the present application is a method of separating a target from a sample composition containing the target, by:

(a) contacting the sample composition with a reactive affinity molecule attached to a phase separating group, the reactive affinity molecule comprising a reactive functional group, and the reactive affinity molecule reacting with the target to form an adduct by forming a covalent bond between the target and the reactive functional group, where the reaction forming the adduct is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond;

(b) separating the adduct from the sample composition;

(c) contacting the adduct with an eluent to regenerate the target and the reactive affinity molecule; and

(d) separating the target from the reactive affinity molecule.

This method, referred to by Appellant as reaction affinity chromatography, relies on the reversible formation of a covalent bond between the target and the reactive functional group of a reactive affinity molecule attached to a phase separating group (e.g. the reversible formation of a covalent bond between the target and a "stationary phase" – to use the language of column

chromatography), separation of the adduct from the sample composition (because the adduct is bound to the stationary phase and the remainder of the sample composition is not), the subsequent spontaneous reversal of the covalent bond formation to regenerate the target *and the reactive affinity molecule* from the adduct (since the reaction is reversible), and the separation of the target from the reactive affinity molecule.

RAC is distinguished from both:
(a) conventional chromatography,
in which *no covalent bond* is formed between the target and the stationary phase (conventional chromatography relies on physical interaction between the target and the stationary phase rather than bond formation),
and the *reaction is reversible*, i.e. the reaction of a target and a stationary phase transiently forms an adduct, but the reaction reverses to regenerate both the target and the stationary phase – so that the stationary phase may be reused for the same separation again and again, and
(b) "covalent chromatography",
in which a *covalent bond is formed* between the target and the stationary phase,
but the reaction forming the covalent bond is *not naturally reversible*, and the covalent bond is broken only by the addition of a reagent *acting at the covalent bond*, and, though the target is regenerated, the stationary phase is not – so that the stationary phase cannot be reused or can be reused only after a separate chemical regeneration.

The non-reversibility of the covalent bond formation in covalent chromatography is illustrated, for example, in the excerpt from *Protein purification methods* (reference 10 of the second IDS). This discusses a classic covalent chromatography technique, the isolation of a thiol-containing protein. Figure 36 (page 336) and the text below it illustrate the technique. In step (a), the protein (target) interacts with a pyridyl disulfide bound to a support (stationary phase), forming a protein bound to the support by a disulfide linkage (adduct). In step (b), the protein (target) is regenerated by contacting the adduct with an excess of a low molecular weight thiol, but note that the stationary phase is not regenerated in this step, what is left when the protein is removed is a thiol bound to the support. The reaction is not reversed, nor is it reversible except only in the sense that the target is released: the target is regenerated, but the stationary phase has gone from a pyridyl disulfide to a thiol. Separate treatment in step (c), reacting the immobilized thiol with pyridyl disulfide, is required to regenerate the pyridyl disulfide on the solid support. Other "covalent chromatography" methods employ similarly irreversible reactions.

It is vital in considering the patentability of this invention to understand the distinction being drawn in the application between a reversible reaction as described and claimed in claim 79 and its dependent claims - a reaction where a target and a substrate react to form a complex, and the reaction can spontaneously reverse to re-form the target and the substrate, and the kind of reaction in which one reactant may be recovered - a reaction where the target and substrate react to form the complex, and the complex may then be chemically modified to recover the target but without regenerating the substrate. While this latter kind of reaction may sometimes be referred to as reversible in the sense that the target may be recovered, it is not reversible within the definition of this application and claim 79, which requires regeneration of both the target and the substrate. Thus, for example, the use of classical protecting groups in organic synthesis is not a reversible reaction within the meaning of this application and the claims under appeal (consider the protection of an alcohol as a tetrahydropyranyl ether by reaction of the alcohol with a dihydropyran: the alcohol may

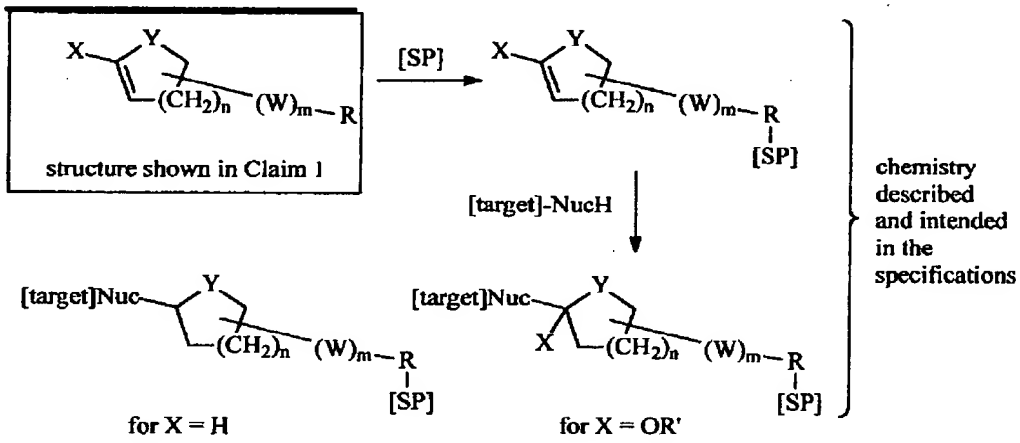
be recovered by treatment with strong acid or a divalent cation, but the dihydropyran is not regenerated).

Thus, while "covalent chromatography" relies on the formation of stable, robust species (e.g. amides, esters, carbamates, disulfides, and acetals) which can only be decomposed by the addition of a reagent acting at the covalent bond, RAC relies on the transient formation of species that are unstable under the conditions of the chromatography. Some of these (hemiacetals, hemiaminals, and the like) are widely recognized as species that cannot be isolated except under special circumstances; others, more apparently stable, contain structural features that cause the adduct to have a transient existence even in the absence of added reagent acting at the covalent bond.

Hylarides

Hylarides discloses a method of isolating a target by conjugating to a solid phase a reagent that contains a heterocyclic 5- or 6-membered ring with a double bond adjacent the heteroatom (e.g. an N-alkyldihydropyrrole, a 2,3-dihydrofuran, a 2,3-dihydrothiophene, or an analogous 6-membered ring) to form a derivatized solid phase, then contacting that derivatized solid phase with a sample containing a target with an available nucleophilic group such that the target bonds to the derivatized solid phase.

This may be illustrated as follows:



Here [SP] represents the solid phase to which the ring compound is bonded, thereby forming the conjugated and immobilized separation reagent. The target is bonded to that reagent by the formation of a covalent bond between a nucleophilic part of the target and the double bond of the ring, bonding the target to the ring at the carbon atom adjacent to the heteroatom. Hylarides states (column 15, lines 47-58) that the covalently bound target may be released in native form from the solid phase by a variety of ways, such as by mildly acid conditions or by divalent cations, and that this process may be accelerated by heat. "In particular, cleavage occurs by decreasing the pH of a solution contacting the solid phase to pH 6.0 or lower, by adding divalent cations such as Zn^{2+} at a concentration at least equal to that of the reagent attached to the solid phase, or by raising the temperature above 23°C in the presence of pH 6.0 or lower."

Looking at Hylarides Example III, the sample composition is a mixture of phenethylmercaptoacetamide (the target), S-acetyl-phenethylthioacetamide (the starting material), bis(phenethylaminocarbonylmethyl)disulfide (a byproduct of the hydrolysis of the starting material), and acetic acid (the other hydrolysis byproduct). The reaction mixture is produced with excess hydroxylamine in methanol/water, so the solution is basic. When the solution passes through the column containing the conjugated 5-methyl-2,3-dihydrofuran (the "stationary phase" of the column), the target bonds to the furan by formation of a covalent bond to form a conjugated *saturated ring* structure 5-methyl-5-(phenethylaminocarbonylmethylthio)tetrahydrofuran, a hemithioketal ("by formation of a covalent adduct", as stated in Hylarides, column 24, lines 31-32). The type of reaction is illustrated in Hylarides' Scheme II, where 6-mercaptopurine reacts with a 5-methyl-2,3-dihydrofuran to form a saturated ring tetrahydrofuran hemithioketal: a similar reaction will occur with the mercapto group of the phenethylmercaptoacetamide. Subsequent lowering of the pH to 4-5 by passing the buffer through the column breaks the S-C bond and regenerates the phenethylmercaptoacetamide.

However, this regeneration or release of the phenethylmercaptoacetamide does not regenerate the dihydrofuran, because the double bond of the dihydrofuran was saturated by the binding with the target and is not dehydrogenated when the pH is lowered and the mercaptan released; instead, what is created in the stationary phase when the pH is lowered is an immobilized decomposition product of the substituted tetrahydrofuran, so that the reaction is *not reversible, and in particular, is not reversible without the addition of a reagent acting at the covalent bond.*

Discussion

The final rejection apparently [because there is no explicit discussion in this rejection of the section of Hylarides that is being referred to - it simply makes the conclusory statement that "The claims are considered to read on Hylarides." (final rejection, page 2, third and second line from bottom)] reasons that the reaction of Hylarides is a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond (the bond between the target and the RFG). Appellant disagrees.

Hylarides, in Example III, illustrates contacting at basic pH (because of the use of an excess of hydroxylamine in the hydrolysis reaction producing the mixture to be separated). There is no indication in Hylarides that the reaction forming the S-C bond in the conjugated 5-methyl-5-(phenethylaminocarbonylmethylthio)tetrahydrofuran is reversible at basic pH (i.e. reversible under the conditions of the contacting); and there is every reason in Hylarides to believe that it is not, because the only method disclosed in Example III to release the phenethylmercaptoacetamide is to lower the pH to 4-5. It is stated in Hylarides, at column 15, lines 43-45, that "Following the step of contacting, it may be desirable to wash the solid phase to remove noncovalently bound compounds." This clearly indicates that the reaction forming the S-C bond is not a reaction reversible under the conditions of the contacting, because if it were, washing would not only remove noncovalently bound compounds, it would also act to remove covalently bound material by reversal of the reaction (once any free phenethylmercaptoacetamide is removed by washing, equilibrium inherent in a reversible reaction would cause decomposition of the conjugated 5-methyl-5-(phenethylamino-carbonylmethylthio)tetrahydrofuran to release more phenethylmercaptoacetamide, so that washing of the derivatized solid phase under the conditions of the contacting would elute phenethylmercapto-acetamide from the derivatized solid phase rather than just removing noncovalently bound

compounds). An illustration that this pH lowering is a direct effect on the atoms/bonds involved in the covalent attachment of the phenethylmercaptoacetamide is that Hylarides discusses elsewhere (e.g. at column 15, lines 46 - 58) not only the reduction of pH to an acid level (below pH 6.0) as a release technique but also as an alternative the use of an excess of a divalent metal cation such as Zn^{2+} – a Lewis acid. It is evident from Hylarides that the reaction between the phenethylmercaptoacetamide and the dihydrofuran is not a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

In fact, the type of reaction taught by Hylarides in Example III is well-known as the formation of a hemithioketal; and while the hemithioketal may in many cases be decomposed under mild conditions to regenerate the mercaptan starting material, the dihydrofuran is not regenerated, and the reaction is therefore not reversible.

Looking more generally at Hylarides, it is clear that Hylarides is not talking about reversible reactions because, in every instance, Hylarides discloses that a separate release/cleavage step is needed to recover the target compound (e.g. column 4, lines 9-14 and lines 42-45, column 5, lines 28-36, etc.). The fact that a separate cleavage step is required distinguishes Hylarides from the method of this invention.

By contrast, this invention is limited to the situation in which the reaction between the target and the RFG is one that *reversibly* forms a covalent bond. For example, paragraph **[0039]** discusses a scheme where thebaine is separated from other opium alkaloids by the use of a nitroso RFG. The nitroso RFG is present on a polymeric resin, which is loaded into a column. The sample composition consisting of thebaine and the other alkaloids is applied to the column, then eluted with a solvent. Because of the reversible covalent bond formation between the thebaine and the nitroso RFG – the reversible formation of a Diels-Alder adduct – passage of the thebaine through the column is delayed, while the other alkaloids, which do not undergo the same reaction, move through the column at the same rate as the eluent.

Hylarides does not anticipate the claims because Hylarides does not disclose a process in which an adduct is formed by a covalent bond-forming reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond. A rejection for anticipation will only stand if the reference discloses every element of the claim, and Hylarides fails to disclose that reversibility of the reaction.

The final rejection responds to Appellant's arguments in four ways; but none of these responses address Appellant's arguments, in particular, none address the non-reversibility of the reactions of Hylarides.

First, the final rejection states that Appellant's arguments "urge patentability based on the allegation that Hylarides discloses washing," but that Appellant's own specification also discloses washing, so that "washing is not considered to be excluded from the open format claims."

Appellant does not urge patentability based solely on the fact that Hylarides discloses washing, Appellant simply makes the point that the non-reversible covalent bond forming reaction of Hylarides is emphasized by Hylarides' suggestion that his covalent product may be washed to remove unbound materials. The final rejection points to paragraphs **[00109]** and **[00119]** as disclosing washing. However, examination of paragraph **[00109]** and following paragraph **[0110]**

will show that the "washing" when the eluent is the same as the loading solvent is simply standard chromatographic elution in which different components elute at different times. As stated in paragraph **[00110]**, "The first portions of the eluent to exit the column will contain the non-thebaine/non-1,3-s-cis diene components of the mixture, since thebaine will be retained as a consequence of the reversible 4+2 cycloaddition reaction. Continued elution will afford eluent containing thebaine." In paragraph **[00119]** it states that after loading "and eluting with sufficient solvent to remove interferents/impurities, the eluent will be modified to include sufficient organic base (e.g. trimethylamine or triethylamine) so as to react with the carboxylic acid groups of the RAMols and make trimethylammonium carboxylate salts. This will result in the desired affinity modification and the enhanced release of the target." There is no inconsistency between the statements in the application that the covalent adduct can be washed and the claim that the adduct must be formed by a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

Second, the final rejection states that Appellant's arguments "urge patentability based on the allegation that Hylarides does not disclose reversing the reaction without the addition of a reagent acting at the covalent bond," but that Hylarides discloses releasing the compound by the use of a pH of 6 or lower and raising the temperature and "This is the same technique that is recited in applicant's claims 119 and 120. As such, Hylarides is considered to disclose reversing the reaction 'without the addition of a reagent acting at the covalent bond.'"

Appellant does not believe that this argument is relevant. First, claims 119 and 120 are not the subject of this appeal. Second, the fact that Hylarides may regenerate his target by the technique of lowering the pH and raising the temperature is of no probative value in considering whether Hylarides discloses reversing the reaction without the addition of a reagent acting at the covalent bond: whether Hylarides' reaction is reversible without the addition of a reagent acting at the covalent bond is to be determined by examination of the reaction as described by Hylarides and not by comparison with Appellant's specification, and examination of the reaction described by Hylarides (formation of a hemithioketal from a dihydrofuran in Example III) leads to the conclusion that this reaction is not reversible without the addition of a reagent acting at the covalent bond. First, the acid (or divalent metal cation) act at the covalent bond; and second, although the mercaptan is released in the presence of acid, this is not the reversal of the bond-forming reaction because the immobilized dihydrofuran is not regenerated.

Third, the final rejection states that Appellant's arguments "urge patentability based on the allegation that Hylarides' amino, sulfhydryl, and carbonyl groups are for binding his reactive compound to the solid phase material. However, a fair reading of Hylarides' column 16, lines 19-59 would indicate that reactive targeting group R' and the solid phase binding group R may be the same groups."

Appellant disagrees. Hylarides states, at column 16, lines 23-32, that "To a solid phase is conjugated, via R, a reagent having the formula (IV): [formula (IV) showing a molecule having terminal R and R' groups] to form a derivatized solid phase. The derivatized solid phase is contacted with a sample solution in which a compound capable of reacting with R' is present, such that the compound bonds to the derivatized solid phase, thereby removing the compound from the sample solution." It is evident from this that if R' and R were the same, as suggested by the final rejection, then both the R' and R groups would react with the solid phase, doubly immobilizing the remainder

of the molecule and leaving no R' group available for bonding with the target compound. While further down the column, Hylarides does state that "R' is a chemically reactive moiety and may be a nucleophile or an electrophile. The selection is generally determined by whether the reactive group on a compound is nucleophilic or electrophilic" and separately that "R' is a chemically reactive moiety which may be a nucleophile or an electrophile. When the solid phase contains available nucleophilic groups, such as a free amino acid, R is an elcctrophilc such as an activated ester. Conversely, when the solid phase contains electrophilic groups, R is a nucleophile", this cannot fairly be taken to imply that R' and R could be same, for the reasons expressed at the beginning of the paragraph - if they were the same, they would both react with the solid phase and there would be no groups available for bonding with the target. In fact, Hylarides, in describing the same molecule of formula (IV) at column 5, line 36 to column 6, line 4, specifically states (column 5, line 63) that "R and R' are not the same.", and makes the same statement in claim 9, completely contradicting the theory expressed in the final rejection.

Finally, the final rejection states that "The remarks appear to use [*sic*, urge] that a nitroso group in Hylarides would not be reversibly reactive. However a nitroso group in Hylarides would appear to be reversibly reactive for all same reason as it would be in applicant's claim 81."

This simply misstates Appellant's position. Appellant nowhere stated that "a nitroso group in Hylarides would not be reversibly reactive." Hylarides does not mention nitroso groups, so there would be no reason for Appellant to make such a statement. If Hylarides were to use a nitroso group as the R' group in a compound of formula (IV), it is possible that it would be reversibly reactive if the target compound were a 1,3-diene, *but Hylarides makes no such disclosure or suggestion.*

Thus claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 are not anticipated by Hylarides.

Further, Hylarides does not render the claims obvious because there is neither disclosure nor suggestion in Hylarides that the covalent bond-forming reaction should be anything other than a reaction that requires the addition of a reaction acting at the covalent bond to regenerate one (but not both) of the reactants. Indeed, a fair reading of Hylarides suggests exactly the contrary: a reversible reaction would be undesirable because washing of the solid phase would reverse the reaction and lose the target material; and the reactions shown by Hylarides are not reversible in the sense used in the present application, that is, regeneration of both reactants and not just regeneration of one, as discussed above. A rejection for obviousness will only stand if the reference suggests the modification and its likelihood of success, and Hylarides offers neither suggestion of a reaction reversible without the addition of a reagent acting at the covalent bond, nor any expectation of success if such a reaction were employed.

The final rejection fails to address these issues - it simply states "However, if a difference exists between the claim and Hylarides, it would reside in optimizing the steps of Hylarides." This is not a proper basis for rejection: in a rejection for obviousness it is incumbent on the Office to demonstrate a *prima facie* case under the statute and decisions interpreting it, not simply to assert obviousness.

Thus claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 are also not obvious over Hylarides.

C. Claims 79, 80, 87-91, 93-94, 106, 107, 114-116, 121, and 122 are not obvious over Hylarides in view of Kohn

Claims 79, 80, 87-91, 93-94, 106, 107, 114-116, 121, and 122 were rejected [two separate rejections were made on pages 5-6 and 6, but the reasons given were identical and the second encompassed the first, so only one response is made] under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn et al., US Patent No. 6,362,008 ("Kohn"). Reversal of this rejection is requested.

The final rejection asserts that "at best, the claims differ from Hylarides in reciting use of methanol as an eluent", and that Kohn discloses that the use of methanol is a known releasing agent for covalent chromatography, so that it would be obvious to use methanol in Hylarides. Appellant disagrees.

First, the combination does not remedy the deficiency of Hylarides in failing to disclose or suggest a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond. Hylarides does not disclose it, and Kohn does not either, because Kohn discloses antibody-analyte binding, which is non-covalent.

Kohn, column 7, lines 59-62, says that "The use of covalent chromatography is similar to other affinity chromatography procedures", but Appellant notes that this section says nothing about methanol. While column 12, lines 16-25 refers to methanol as one of three possible solvents for the release of bound T-2 from antibodies on a matrix, this is not covalent chromatography, it is antibody-analyte affinity chromatography, which is widely recognized not to involve covalent bonding. As a person of skill in the art would recognize, high concentrations of methanol, ethanol, or acetonitrile (the three solvents mentioned in the cited section) denature most proteins, including antibodies, so their use as release agents for affinity chromatography is understandable. However, there is nothing in Kohn that suggests that methanol would be useful as an eluent for covalent chromatography, still less that it would be useful as an eluent for the reaction affinity chromatography of this invention.

Appellant notes that the resin used for the separation of column 12, lines 16-25 is not a matrix of the type disclosed in column 7, such as a thiol-containing matrix, it is an activated Sepharose 4B gel, which is a simple gel-permeation chromatography medium (and indeed Kohn suggests that the antibodies can be bound to matrices as simple as a glass plate, *see* column 12, line 24).

Further, there is nothing in Hylarides or Kohn to suggest the desirability of the combination – Hylarides performs his covalent chromatography separations with acid or divalent metal ion Lewis acid, and Kohn his affinity chromatography separations with an antibody-denaturing solvent such as methanol, ethanol, or acetonitrile; and there is nothing in either reference to suggest the substitution of methanol for Hylarides' reagents (and every reason from the art to believe that the substitution would not be useful since the reactions are of totally different types).

The final rejection, in responding to Appellant's arguments, states that "The remarks urge that Kohn is not pertinent because it discloses activated Sepharose. However, 'activated' is a synonym for 'reactive'. As such, Kohn is considered to be pertinent to reactive chromatography."

Appellant disagrees. Kohn is not pertinent because it disclose antibody-analyte chromatography (not involving covalent bond formation), in which the analyte is recovered by denaturing of the antibody (a non-reversible reaction). As for "activated Sepharose" being the reactive affinity molecule of the claims, a quick examination of Kohn shows that this is simply not so. See Kohn, column 10, section V. Affinity Matrix Comprising Immobilized Anti-T2 Monoclonal Antibody, lines 1-32, in particular lines 8-17 "This antibody solution [the anti-T2 antibody solution] is added to 2.5 g of cyanogen bromide-activated Sepharose-4B (Sigma) which has been incubated previously in 8.0 ml of 0.001 M HCl overnight. After the Sepharose and the antibody solution are allowed to react for 1 hour, the unbound sites of the antibody bound gel are blocked by incubating the solid phase sorbant material with 01 M Tris, pH 8.3 for 1 hour. The combination of the monoclonal antibody immobilized onto the solid phase sorbant material form an affinity matrix which then was used in volumes of 0.3-0.5 mL." Kohn's activated Sepharose is nothing more than the solid phase onto which the antibody (the reactive unit in the antibody-analyte chromatography) is immobilized; and the only reaction involving the activated Sepharose is the one in which the monoclonal antibody is bound to it. Kohn is not pertinent to reactive affinity chromatography.

Thus claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 are not obvious over Hylarides in view of Kohn.

D. Claims 81, 123, and 128 are not obvious over Hylarides in view of Schössler or Carron and Sohar, or over Hylarides in view of Kohn further in view of Schössler or Carron and Sohar

Claims 81, 123, and 128 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of either Schössler et al., US Patent No. 4,822,681 ("Schössler") or Carron et al., PCT Publication No. WO 98/59234 ("Carron") and Sohar et al., US Patent No. 3,894,026 ("Sohar"). Claims 81, 123, and 128 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of either Schössler or Carron and Sohar. Reversal of these rejections is requested.

Hylarides in view of Schössler or Carron and Sohar

It is unclear whether the final rejection is one over Hylarides in view of Schössler or (Carron and Sohar) [i.e., Hylarides in view of Schössler, or Hylarides in view of Carron and Sohar] or over Hylarides in view of (Schössler or Carron) and Sohar [i.e., Hylarides in view of Schössler and Sohar, or Hylarides in view of Carron and Sohar]. The argument will address the three possibilities arising from this lack of clarity.

The final rejection asserts that "at best, the claims differ from Hylarides in reciting use of a nitroso group and targeting a 1,3-diene group" and that the secondary references fill this gap. Appellant disagrees.

With respect to Schössler, the final rejection states that Schössler (column 3, lines 20-22) discloses that a nitroso group is interchangeable with Hylarides' (column 32, lines 60-63) amino, carbonyl, and sulfhydryl groups. Schössler discloses the formation of polymer solid body surfaces with functionalized silyl groups and that these silyl groups may be functionalized with, *inter alia*, nitroso groups as well as amino, carbonyl, and sulfhydryl groups; however, these surface groups are by no means the equivalent of the groups disclosed at column 32, lines 60-63, of Hylarides. The

groups R claimed at column 32, lines 60-63 of Hylarides are not the reactive functional groups of a reactive affinity molecule, they are the means by which Hylarides' dihydrofuran or other heterocycle (the reactive portion of the molecule) is attached to the solid phase support. *See* Hylarides at column 15, lines 34-36: "The step of conjugating the reagent to the solid phase attaches the former to the latter via R, thereby forming a derivatized solid phase," and *see* throughout Hylarides, where it is made clear that the bonding of the "target" occurs by covalent bonding to the carbon atom adjacent the heteroatom of the heterocycle. Referring to Example III of Hylarides, the dihydrofuran is attached through an acetic acid to an N-hydroxysulfosuccinimidate, and it is this portion of the molecule that reacts with the aminohexyl Sepharose to link the dihydrofuran to the resin. It is the dihydrofuran that reacts with the phenethylmercaptoacetamide, not the sulfosuccinimidate. Thus Hylarides' amino, carbonyl, and sulfhydryl R groups are not groups to which a nitroso group of Schössler is analogous, they are if anything analogous to the alkoxy, phenoxy, or halogen R groups of Schössler.

Further, although Schössler discloses the functionalizing of the surfaces of polymer bodies with groups including nitroso groups, there is no suggestion in Schössler that the reactions of these functional groups with target molecules should be reversible without the addition of a reagent acting at the covalent bond. In fact, Schössler is to the contrary: Schössler's general discussion is of the formation of surfaces "upon which proteins, nucleic acids, low-molecular ligands, cells, microorganisms and other biological materials can be bound with *high stability* and yield, as well as biocompatibility" (column 2, lines 65-68, emphasis added); and Schössler's discussion of reversibility (column 5, lines 3-12) refers to the formation of disulfide groups which can be cleaved "by means of the employment of suitable reducing agent," clearly illustrating bonding that is not reversible without the addition of a reagent acting at the covalent bond.

Finally, there is nothing in either Hylarides or Schössler suggesting a 1,3-diene as a target (claim 81), or ergosterol, thebaine or vitamin D as a target (claim 123), or thebaine as a target (claim 128) or suggesting the desirability of the proposed combination, nor does the combination remedy the deficiency of Hylarides in failing to disclose or suggest a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond. Hylarides does not disclose it, and Schössler does not either, because Schössler, like Hylarides, discloses non-reversible binding.

With respect to claim 128, which discloses only the contacting, the argument is essentially the same as for the chromatography claims 81 and 123: neither reference discloses nor suggests thebaine as the target and a nitroso group (still less a modified nitrosobenzene as claimed in claim 128) as the reactive affinity molecule.

Thus Schössler fails to remedy the deficiency of Hylarides in not showing a nitroso group as reactive functional group and 1,3-diene as target, and the combination does not meet the claims.

With respect to Carron, the argument is the same as for Schössler. While Carron discloses a variety of reactive functional groups (including the nitroso group mentioned in the final rejection) that may interact with analytes, these groups – precisely because they do interact with the analytes – are not analogous to the carbonyl R group of Hylarides, which is a group bonding to the solid phase. Further, there is nothing in either Hylarides or Carron suggesting the desirability of the proposed combination.

Thus Carron also fails to remedy the deficiencies of Hylarides, and the combination does not meet the claims.

The final rejection cites Sohar as disclosing the chromatographic purification of thebaine, a 1,3-diene. However, Sohar discloses only conventional techniques and does not disclose the use of methods involving reversible formation of covalent bonds. For example, the final rejection refers to column 4, lines 25-28, disclosing liquid chromatography of thebaine to assay purity. No details are given at that location, but column 3, lines 48-51 discusses the use of a 2 IPAX column coated with 2-cyanoethyl ether and eluting with 10% ethanol/hexane 25% saturated with 2-cyanoethyl ether. Such a support is not known or expected to react with thebaine or 1,3-dienes at all, much less reversibly: chromatographic media of this type are known to act by the physical partitioning of a substance between a liquid-like stationary phase and a liquid mobile phase. The other method cited (column 4, lines 55-57) involves alumina, to which no reversible or non-reversible reaction with thebaine or other 1,3-dienes is expected: chromatography on alumina involves absorption/desorption to the alumina. No specificity associated with chemical reaction is expect or found; and of course Sohar does not mention nitroso groups or reversible covalent bonding. Further, there is nothing in any of Hylarides, Schössler, Carron, or Sohar suggesting the desirability of either of the proposed combinations (Hylarides in view of Schössler and Sohar and Hylarides in view of Carron and Sohar) because the techniques are so different that a person of ordinary skill in the art would find no motivation for the combination, nor expectation of success, in the references.

Thus Sohar fails to remedy the deficiencies of both Hylarides in view of Schössler and Hylarides in view of Carron, and the combination does not meet the claims.

Thus claims 81, 123, and 128 are not obvious over Hylarides in view of Schössler or Carron and Sohar.

Hylarides in view of Kohn further in view of Schössler or Carron and Sohar

Claims 81, 123, and 128 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of either Schössler or Carron and Sohar. Reversal of this rejection is requested.

The final rejection asserts that "at best, the claims differ from Hylarides and Kohn in reciting use of a nitroso group and targeting a 1,3-diene group" and that the secondary references fill this gap. Appellant disagrees.

As discussed above in the discussion of the rejection of claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 (subsection C. above), there is nothing in Hylarides or Kohn to suggest the desirability of the combination proposed – the two methods are quite different, covalent chromatography released with protic acid or Lewis acid, and affinity chromatography released with an antibody-denaturing agent such as an alcohol or acetonitrile, and neither discloses a covalent bond-forming reaction reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

The deficiencies of the proposed combination of Hylarides with Schössler or Carron and Sohar are discussed immediately above, and the argument here is the same, because Kohn (for the

reasons discussed above with respect to the rejection over Hylarides and Kohn alone) adds nothing to Hylarides.

Schössler discloses the formation of polymer solid body surfaces with functionalized silyl groups and that these silyl groups may be functionalized with, *inter alia*, nitroso groups as well as amino, carbonyl, and sulfhydryl groups. However, Hylarides' amino, carbonyl, and sulfhydryl R groups are not groups to which a nitroso group of Schössler is analogous, they are if anything analogous to the alkoxy, phenoxy, or halogen R groups of Schössler. Also, there is no suggestion in Schössler that the reactions of these functional groups with target molecules should be reversible without the addition of a reagent acting at the covalent bond. Further, there is nothing in either Hylarides or Schössler suggesting the desirability of the proposed combination. With respect to Carron, the argument is the same as for Schössler. While Carron discloses a variety of reactive functional groups (including the nitroso group mentioned by the final rejection) that may interact with analytes, these groups – precisely because they do interact with the analytes – are not analogous to the carbonyl R group of Hylarides, which is a group bonding to the solid phase. Further, there is nothing in either Hylarides or Carron suggesting the desirability of the proposed combination. *See* the previous discussion for detail, which is omitted here in the interest of brevity. Thus neither Schössler nor Carron is combinable with Hylarides, and the combinations proposed fail to meet the claims. While Sohar discloses the chromatographic purification of thebaine, a 1,3-diene, Sohar discloses only conventional techniques and does not disclose the use of methods involving reversible formation of covalent bonds. No specificity associated with chemical reaction is expect or found; and of course Sohar does not mention nitroso groups or reversible covalent bonding. Further, there is nothing in any of Hylarides, Schössler, Carron, or Sohar suggesting the desirability of the proposed combination. Thus Sohar fails to remedy the deficiencies of both Hylarides in view of Schössler and Hylarides in view of Carron, and the combination does not meet the claims. These deficiencies are not remedied by the addition of Kohn, because Kohn relates to affinity chromatography, not involving formation of covalent bonds, and therefore (a) is not combinable because the techniques are non-analogous and the proposed solvent substitution of the combination is non-functional, and (b) still fails to meet the claims because none of the documents remedy the basic deficiency of Hylarides in failing to disclose or suggest a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

Thus claims 81, 123, and 128 are not obvious over Hylarides in view of Schössler or Carron and Sohar, or over Hylarides in view of Kohn further in view of Schössler or Carron and Sohar.

E. Claim 91 is not obvious over Hylarides in view of Stevens and Schössler, or over Hylarides in view of Kohn further in view of Stevens and Schössler

Claim 91 was rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Stevens et al, US Patent No. 4,927,539 ("Stevens") and Schössler. Claim 91 was rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn and further in view of Stevens and Schössler. Reversal of these rejections is requested.

Hylarides in view of Stevens and Schössler

The final rejection asserts that "at best, the claim differs from Hylarides in reciting use of a macroreticular polymer", and that Stevens discloses that a macroporous polymer has a higher capacity and Schössler discloses that reactive supports are conventionally macroporous, so that it

would have been obvious to use a macroreticular polymer in the method of Hylarides, making the claim obvious. Appellant disagrees.

While macroreticular polymers have a higher capacity than non-macroporous polymers and Schössler discloses that reactive supports are frequently macroporous (though Schössler certainly discloses non-macroporous reactive supports - *see* column 10, lines 22-23 where "carbon and silicon granular preparations and the like, including glass plates" are mentioned as alternative substrates); however, neither Stevens nor Schössler, alone or in combination, remedy the deficiencies of Hylarides in failing to disclose or suggest a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond; so that the combination of Hylarides and Stevens (and Schössler) fails to meet the claim.

Thus claim 91 is not obvious over Hylarides in view of Stevens and Schössler.

Hylarides in view of Kohn further in view of Stevens and Schössler

The final rejection asserts that "at best, the claim differs from Hylarides in view of Kohn in reciting use of a macroreticular polymer", and that Stevens discloses that a macroporous polymer has a higher capacity and Schössler discloses that reactive supports are conventionally macroporous, so that it would have been obvious to use a macroreticular polymer in the method of Hylarides and Kohn, making the claim obvious. Appellant disagrees.

As discussed above in the discussion of the rejection of claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 (subsection C. above), there is nothing in Hylarides or Kohn to suggest the desirability of the combination proposed – the two methods are quite different, covalent chromatography released with protic acid or Lewis acid, and affinity chromatography released with an antibody-denaturing agent such as an alcohol or acetonitrile, and neither discloses a reaction reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

In addition to these deficiencies, neither Stevens nor Schössler, alone or in combination, remedy the deficiencies of Hylarides and Kohn (assuming even that the combination could properly be made) in failing to disclose or suggest a covalent bond-forming reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond; so that the combination of Hylarides, Kohn, and Stevens (and Schössler) fails to meet the claim.

Thus claim 91 is not obvious over Hylarides in view of Kohn further in view of Stevens and Schössler.

F. Claims 99, 101, and 103-105 are not obvious over Hylarides in view of Carron or Duran, or over Hylarides in view of Kohn further in view of Carron or Sohar

Claims 99, 101, and 103-105 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Carron or Duran et al., PCT International Publication No. WO 99/16907 ("Duran"). Claims 99, 101, and 103-105 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of Carron or Duran. Reversal of these rejections is requested.

Hylarides in view of Carron or Duran

The final rejection asserts that "at best, the claims differ from Hylarides in reciting use of a reactivity modifier group", that Carron "discloses modifiers such as amines influence the reactivity between the reactive functional group and the analyte", and that Duran "discloses ionic compounds such as amines attract target molecules", so that it would be obvious to use a modifier in Hylarides. Appellant disagrees.

With respect to Carron, the basic argument is as made in subsection D. above, and repeated here. While Carron discloses a variety of reactive functional groups (including the nitroso group mentioned in the final rejection) that may interact with analytes, these groups – precisely because they do interact with the analytes – are not analogous to the carbonyl R group of Hylarides, which is a group bonding to the solid phase.

While Carron discloses that the reactivity of reactive functional groups can be modified by the use of reactivity modifier groups, Carron fails to remedy the previously-mentioned basic deficiency of Hylarides in failing to disclose or suggest a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond. Further, there is nothing in either Hylarides or Carron suggesting the desirability of the proposed combination.

Thus Carron also fails to remedy the deficiencies of Hylarides, and the combination if made does not meet the claims.

While Duran discloses the use of charged groups, these charged groups are put on a surface in order to attract target molecules through ion-pairing effects. *See* Duran at page 4, lines 18-19, where the attractive force is "between attractive (e.g. ionic) groups on the bound reagent and oppositely charged groups on the target. Once attracted to the bound reagent, and in turn to the surface, the target molecule can be thermochemically coupled to the bound reagent by reaction between the reactive groups of the bound reagent and appropriate functional groups on the target molecule. The thermochemically reactive groups and the ionic groups can either be on the same polymer or on different polymers that are coimmobilized on the surface." Thus, Duran's ionic groups are not reactivity modifiers, because they are used solely for ionic attraction and because they can be on different polymers, and the sections cited by the final rejection are not to the contrary - indeed, they emphasize this very point. Also, in the purification of thebaine (paragraphs **[0039]** and **[00116]** and Figure 5), affinity of the thebaine for the reactive functional group is increased when the reactivity modifier group and the thebaine are both positively charged, which is directly contradictory to the effect of Duran. Further, Duran relates to a method for irreversible covalent attachment of oligos to surfaces.

There is no motivation in either Hylarides or Duran for the combination proposed by the final rejection and, even if such a combination were made, it would not meet the claims because Duran fails to remedy the deficiency of Hylarides in failing to disclose or suggest a reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond, and because Duran does not disclose reactivity modifier groups.

Thus Duran also fails to remedy the deficiencies of Hylarides, and the combination if made does not meet the claims.

Thus claim 91 is not obvious over Hylarides in view of Carron or Duran.

Hylarides in view of Kohn further in view of Carron or Duran

The final rejection asserts that "at best, the claims differ from Hylarides in view of Kohn in reciting use of a reactivity modifier group", that Carron "discloses modifiers such as amines influence the reactivity between the reactive functional group and the analyte", and that Duran "discloses ionic compounds such as amines attract target molecules", so that it would be obvious to use a modifier in Hylarides. Appellant disagrees.

As discussed above in the discussion of the rejection of claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 (subsection C. above), there is nothing in Hylarides or Kohn to suggest the desirability of the combination proposed – the two methods are quite different, covalent chromatography released with protic acid or Lewis acid, and affinity chromatography released with an antibody-denaturing agent such as an alcohol or acetonitrile, and neither discloses a reaction reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

The deficiencies of the proposed combination of Hylarides with Carron or Duran are discussed immediately above, and the argument here is the same, because Kohn (for the reasons discussed above with respect to the rejection over Hylarides and Kohn alone) adds nothing to Hylarides.

The deficiencies of the combination of Hylarides and Kohn have been pointed out previously in the discussion of the rejection of claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 (subsection C. above), and that argument is incorporated here by reference for brevity. In addition to these deficiencies, neither Carron nor Duran, alone or in combination, remedy the deficiencies of Hylarides and Kohn (assuming that the combination could even properly be made) in failing to disclose or suggest a covalent bond-forming reaction that is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond ; so that the combination of Hylarides, Kohn, and Carron or Duran fails to meet the claims.

Thus claim 91 is not obvious over Hylarides in view of Kohn further in view of Carron or Duran.

G. Claims 108 and 109 are not obvious over Hylarides in view of Schössler or Carron, or over Hylarides in view of Kohn further in view of Schössler or Carron

Claims 108 and 109 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of either Schössler or Carron. Claims 108 and 109 were rejected under 35 USC 103(a) as being unpatentable over Hylarides in view of Kohn further in view of either Schössler or Carron. Reversal of these rejections is requested.

Hylarides in view of Schössler or Carron

The final rejection asserts that "at best, the claims differ from Hylarides in reciting use of a nitroso group", that Schössler discloses that a nitroso group is interchangeable with Hylarides' amino, sulfhydryl, or carbonyl groups, and that Carron discloses that a nitroso group is

interchangeable with Hylarides' carbonyl group, so that it would be obvious to use a nitroso group in Hylarides. Appellant disagrees.

The argument with respect to these claims is essentially the same as the argument with respect to claims 81, 123, and 128 discussed in subsection **D.** above, except for the discussion of the 1,3-diene as target.

Schössler discloses the formation of polymer solid body surfaces with functionalized silyl groups and that these silyl groups may be functionalized with, *inter alia*, nitroso groups as well as amino, carbonyl, and sulfhydryl groups. However, Hylarides' amino, carbonyl, and sulfhydryl R groups are not groups to which a nitroso group of Schössler is analogous, they are if anything analogous to the alkoxy, phenoxy, or halogen R groups of Schössler. Also, there is no suggestion in Schössler that the reactions of these functional groups with target molecules should be reversible without the addition of a reagent acting at the covalent bond. Further, there is nothing in either Hylarides or Schössler suggesting the desirability of the proposed combination.

With respect to Carron, the argument is the same as for Schössler. While Carron discloses a variety of reactive functional groups (including the nitroso group mentioned in the final rejection) that may interact with analytes, these groups – precisely because they do interact with the analytes – are not analogous to the carbonyl R group of Hylarides, which is a group bonding to the solid phase. Further, there is nothing in either Hylarides or Carron suggesting the desirability of the proposed combination. *See* the discussion in subsection **C.** for detail, which is omitted here in the interest of brevity.

Neither Schössler nor Carron is combinable with Hylarides, and the combinations proposed fail to meet the claims.

Thus claims 108 and 109 are not obvious over Hylarides in view of Schössler or Carron.

Hylarides in view of Kohn further in view of Schössler or Carron

The final rejection asserts that "at best, the claims differ from Hylarides in view of Kohn in reciting use of a nitroso group", that Schössler discloses that a nitroso group is interchangeable with Hylarides' amino, sulfhydryl, or carbonyl groups, and that Carron discloses that a nitroso group is interchangeable with Hylarides' carbonyl group, so that it would be obvious to use a nitroso group in Hylarides. Appellant disagrees.

As discussed above in the discussion of the rejection of claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 (subsection **C.** above), there is nothing in Hylarides or Kohn to suggest the desirability of the combination proposed – the two methods are quite different, covalent chromatography released with protic acid or Lewis acid, and affinity chromatography released with an antibody-denaturing agent such as an alcohol or acetonitrile, and neither discloses a reaction reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond.

The deficiencies of the proposed combination of Hylarides with Schössler or Carron have been discussed before in the discussion of the rejection of claims 81, 123, and 128 (subsection **D.**

above), and the argument here is the same, because Kohn (for the reasons discussed above with respect to the rejection over Hylarides and Kohn alone) adds nothing to Hylarides.

Hylarides' amino, carbonyl, and sulfhydryl R groups are not groups to which a nitroso group of Schössler is analogous, they are if anything analogous to the alkoxy, phenoxy, or halogen R groups of Schössler; there is no suggestion in Schössler that the reactions of these functional groups with target molecules should be reversible without the addition of a reagent acting at the covalent bond; and there is nothing in either Hylarides or Schössler suggesting the desirability of the proposed combination. While Carron discloses a variety of reactive functional groups (including the nitroso group mentioned by the final rejection) that may interact with analytes, these groups – precisely because they do interact with the analytes – are not analogous to the carbonyl R group of Hylarides; and there is nothing in either Hylarides or Carron suggesting the desirability of the proposed combination. Thus neither Schössler nor Carron is combinable with Hylarides, and the combinations proposed fail to meet the claims.

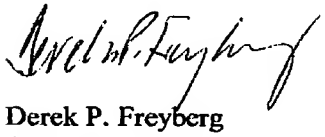
The deficiencies of the combination of Hylarides and Kohn have been pointed out previously in the discussion of the rejection of claims 79, 80, 87-91, 93, 94, 106, 107, 114, 121, and 122 (subsection C. above), and that argument is incorporated here by reference for brevity. In addition to these deficiencies, neither Schössler nor Carron, alone or in combination, remedy the deficiencies of Hylarides and Kohn (assuming that the combination could properly be made); so that the combination of Hylarides, Kohn, and Schössler or Carron fails to meet the claims.

Thus claims 108 and 109 are not obvious over Hylarides in view of Schössler or Carron, or over Hylarides in view of Kohn further in view of Schössler or Carron.

Conclusion

Claims 79, 80, 87-91, 93, 94, 99, 101, 103-109, 114-116, and 121-123 comply with 35 USC 112, ¶1 and are not drawn to new matter; and none of claims 79-81, 87-91, 93, 94, 99, 101, 103-109, 114-116, 121-123, and 128 are either anticipated by or obvious over the references and combinations of references cited in the final rejection. Reversal of the rejections is respectfully requested.

Respectfully submitted,



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27 December 2004

(viii) Claims appendix

79. A method of separating a target from a sample composition containing the target, comprising the following steps:

(a) contacting the sample composition with a reactive affinity molecule attached to a phase separating group, the reactive affinity molecule comprising a reactive functional group, and the reactive affinity molecule reacting with the target to form an adduct by forming a covalent bond between the target and the reactive functional group, where the reaction forming the adduct is reversible under the conditions of the contacting without the addition of a reagent acting at the covalent bond,

(b) separating the adduct from the sample composition;

(c) contacting the adduct with an eluent to regenerate the target and the reactive affinity molecule; and

(d) separating the target from the reactive affinity molecule.

80. The method of claim 79 where the reactive functional group comprises a group chosen from N=N, C=C, C=O, N=O, C=N, C=S, and C≡C.

81. The method of claim 79 where the target comprises a 1,3-diene and the reactive functional group comprises a nitroso group.

87. The method of claim 79 where the reactive affinity molecule is attached to the phase separating group by a covalent bond, chemisorption, or ion-pairing.

88. The method of claim 79 where the phase separating group is a solid.

89. The method of claim 88 where the solid is chosen from polymers, silica, alumina, and carbon.

90. The method of claim 89 where the solid is a polymer.

91. The method of claim 90 where the solid is a macroreticular polymer.

93. The method of claim 90 where the solid is chosen from polyacrylates and polystyrene.

94. The method of claim 88 where the solid is a stationary phase of a chromatographic column.

99. The method of claim 79 where the reactive affinity molecule further comprises a reactivity modifier group.

101. The method of claim 99 where the reactivity modifier group comprises a basic group chosen from amines, heteroaryl amines, carboxylates, phenolates, phosphate anions, and phosphonate anions.

103. The method of claim 99 where the reactivity modifier group is chosen from hydroxyl groups, amine groups, monoalkylamine groups, dialkylamine groups, and alkoxy groups.

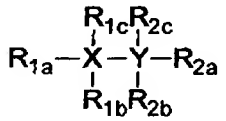
104. The method of claim 99 where the reactivity modifier group alters a property of the reactive functional group chosen from electronic characteristics, steric availability, and chirality.

105. The method of claim 99 where the eluent changes the equilibrium constant of the reaction by modifying the reactivity modifier group.

106. The method of claim 79 where the reactive affinity molecule further comprises a framework group.

107. The method of claim 106 where the framework group comprises a group chosen from alkyl groups, aryl groups, and heteroaryl groups.

108. The method of claim 79, where the reactive affinity molecule comprises a group of formula



where R_{1a}, R_{1b}, R_{1c} R_{2a}, R_{2b} and R_{2c} are each independently absent or are chosen from H, alkyl groups, aryl groups, heteroaryl groups, framework groups, reactivity modifier groups, framework groups with reactivity modifier groups, a direct bond between X and Y, and a direct bond to a phase separating group; and

where X and Y are each independently chosen from C, O, N, and S, and each independently may have a positive or a negative charge.

109. The method of claim 108 where the reactive affinity molecule comprises a group chosen from $R_{1a}(R_{1b})C=C(R_{2a})R_{2b}$, $R_{1a}(R_{1b})C=O$, $R_{1a}(R_{1b})C=N\text{-}R_{2a}$, and $R_{1a}\text{-}N=O$.

114. The method of claim 79, where the reaction comprises the formation of at least two covalent bonds.

115. The method of claim 79 where the eluent is chosen from water, alcohols, hydrocarbons, and ethers.

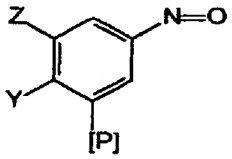
116. The method of claim 115 where the eluent is chosen from methanol, ethanol, propanol, isopropanol and butanol.

121. The method of claim 79 where the half-life of the reaction is about 4 hours or less at 25^0C under the contacting conditions.

122. The method of claim 79 where the step of contacting the adduct with the eluent also separates the target from the reactive affinity molecule.

123. The method of claim 79 where the target is chosen from ergosterol, thebaine, and vitamin D.

128. A method for isolating thebaine from a sample composition, comprising contacting the sample composition with a reactive affinity molecule of the formula:



where Y and Z are each independently chosen from H, alkyl groups, aryl groups, heteroaryl groups, framework groups, reactivity modifier groups, and framework groups with reactivity modifier groups; and

[P] is a phase separating group.